UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,514	07/16/2003	Ricardo M. Attar	D0287 NP	3956

23914 7590 07/10/2007

LOUIS J. WILLE
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
07/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/620,514	ATTAR ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,18 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the appeal brief filed on March 20, 2007, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below.

PETER PARAS, JR.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Applicant has filed amended claims, November 13, 2006. The amendment has been entered. Claim 18 is amended. Claims 14-17, 20 are cancelled.

Claims 1-13, 18, 19 are under consideration.

Withdrawn Rejection

35 U.S.C. § 112, 2nd parag.

Applicant's arguments, see page 12 of the Appeal Brief, filed March 20, 2007, with respect to the rejection of claim 18 as lacking antecedent basis have been fully considered and are persuasive. Applicant has amended the claim from "non-human mammal" to "mouse." The rejection of claim 18 has been withdrawn.

New/Maintained Rejections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 3, 4, 6, 8, 10, 18, 19 remain rejected in modified form under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

Applicant has provided a rebuttal in the Appeal Brief, filed March 20, 2007 regarding the rejection of the claims under 101. Response to Applicant's rebuttal is provided following the rejection.

The claims are broadly drawn to transgenic mice whose genome comprises a nucleic acid construct, wherein said construct comprises nucleic acid sequences encoding an androgen receptor and a reporter protein operably linked to a promoter comprising an androgen response element, wherein said mice express the reporter protein and androgen receptor in at least one tissue selected from the group consisting of lung, heart, liver, testis, bone, prostate, and kidney; a cell obtained from said transgenic mouse; a nucleic acid construct used to generate said mouse; a method of making said mouse; and a method of screening for a modulator of the androgen receptor, using said mouse.

While the art provides guidance for one type of mouse that is readable on the claims (a transgenic mouse comprising a Pb-mAR transgene construct, see Enablement and 103 rejections for more details), neither the specification provides guidance for the utility of the full breadth of mice comprising a transgene construct comprising nucleic acid sequences that encode a reporter protein and androgen receptor from any species of animal operably linked to any androgen response element. More particularly, with regard to the claims being drawn to the mouse described in the specification, wherein the mouse comprises in its transgene construct a 2XDR-1 androgen response element (e.g. claim 3), the specification does not provide specific and substantial guidance for the use of these mice.

The specification indicates that the transgenic mouse comprising a 2XDR-1 androgen response element is used to assess tissue specific activity of the androgen receptor. Such model could be used to study the tissue selective activity of pharmacological agents as well as the activity of the androgen receptor in different organs of males and females (specification, page 5, 2nd parag.). The specification also indicates that the transgenic mice comprising a 2XDR-1 androgen response element can be used in identifying, developing, and optimizing biological and chemical moieties that modulate the activity of the androgen receptor. Such moieties can be used for the treatment of prostate cancer, andropausia, and hormone replacement (specification, page 11, lines 21-25). The specification provides no additional uses for the cells and nucleic acid construct used to make the mouse and thus, the utility of these products depend on the transgenic mouse comprising a 2XDR-1 androgen response element.

With regard to the specification indicating the transgenic mice comprising a 2XDR-1 androgen response element are used to study the activity of the androgen receptor in different organs of males and females, the asserted utility lacks specific and substantial utility of the claimed invention. According to the Revised Utility Examination Guidelines published December 21, 1999 in the Federal Register, Volume 64, Number 244, pages 71441-71442 the following definitions for specific and substantial utility applies.

A specific utility is one that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not

substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility.

As such, determining what biological activity occurs following protein overexpression is a general use of transgenic overexpression mice and is not a specific and substantial used of the claimed mice. It is noted that an artisan cannot necessarily predict that any phenotype exhibited by a transgenic animal is necessarily a result of the transgene construct, and thus, an artisan cannot reasonably predict what utility a transgenic animal has. This issue will be discussed further in the Enablement rejection.

With regard to the asserted utility of the transgenic mouse comprising a 2XDR-1 androgen response element being used to study the selective activity of pharmacological agents, the specification does not provide guidance that the transgenic mouse comprising a 2XDR-1 androgen response element exhibited any phenotype and thus, the asserted use of the transgenic mouse comprising a 2XDR-1 androgen response element to study selective activity of pharmacological agents is not readily apparent. Similarly, identifying, developing, or optimizing biological or chemical moieties that modulate the activity of the androgen receptor such that the moieties can be used in treatment of a disease or disorder is not readily apparent. Further, the specification also does not teach that the transgenic mouse comprising a 2XDR-1 androgen response element exhibit any biological response to the overexpression of androgen receptor, such that the transgenic mouse comprising a 2XDR-1 androgen response element can be used to determine the activity of androgen receptor in male and female animals. The specification teaches that three mice from line 26 were

obtained (one non-transgenic and two transgenic) and that the luciferase was expressed in the genitals of the transgenic mice. To confirm that the transgene was androgen dependent, one of the transgenic mice was castrated and loss of luminescence in the castrated mouse confirmed androgen dependent expression of the luciferase (specification, page 13, 2nd parag.). The specification also teaches that luciferase expression depended on androgens by injecting 2 mice with testosterone. The mice exhibited increased total photon emission following testosterone treatment (specification, page 13, 4th parag.). While the specification indicates that luciferase was overexpressed in the mice, the specification does not indicate what biological response the transgenic mouse comprising a 2XDR-1 androgen response element had such that the mice exhibit any phenotype related to overexpression of androgen receptor. Further, because there was no response to the overexpression of androgen receptor, the use of the mouse to study selective activity of pharmacological agents is not readily apparent. This issue is discussed further in the Enablement rejection. As such, the transgenic mouse comprising a 2XDR-1 androgen response element lacks specific and substantial utility.

Because the transgenic mouse comprising a 2XDR-1 androgen response element have no specific and substantial utility, the cells, the transgene construct, the methods of making the transgenic mouse comprising a 2XDR-1 androgen response element and the method of using the transgenic mouse comprising a 2XDR-1 androgen response element also lack specific and substantial utility.

Applicant's arguments filed March 20, 2007 have been fully considered but they are not persuasive.

Applicant indicates that the specification, as filed, provides a credible, specific, and substantial use for the claimed invention. Independent claims 1 and 11 require that the androgen receptor nucleic acid is expressed in the transgenic mouse in at least one tissue selected from the group consisting of lung, heart, liver, testis, bone, prostate, and kidney, such that the mouse has enhanced expression of androgen receptor relative to a wild type mouse in the at least one tissue. Accordingly, the transgenic mouse of the invention has enhanced expression of androgen receptor relative to wild type mouse in the at least one tissue (Appeal Brief, page 8, 2nd parag. under point 2). In response, as indicated in the Enablement rejection, below, an increased level of rat AR in the transgenic mouse's cells does not provide specific and substantial utility for the mouse. This stems from the fact the mice described in the specification do not exhibit any phenotype related to the overexpression of rat AR. According to Racay, Franz et al., and Jakel et al., Enablement, below, the art teaches that transgenic animals that even after determining what components in a transgene construct should be used to generate a transgenic animal, the animal can exhibit unexpected or no phenotype and the cause of these unexpected or no phenotypes stems from factors unrelated to the transgene. These include interspecies differences, genetic background of the host, and environment. As this applies to the instant invention, while it may be that the rat AR protein has activity, as evidenced by the fact that transgenic mice injected with testosterone showed an increased amount of luciferase (specification, page 13, lines

26-32), rat AR protein appears only to bind to the artificial construct, 2XDR-1, and does not appear to bind to and activate regulatory regions of other genes in the mouse genome, as evidenced by the lack of phenotype of the mouse. Without further guidance from the specification, based on the teachings of Racay, Franz et al., and Jakel et al., the lack of phenotype has been interpreted as some unrelated factor(s), such as background of the host or cellular environment, that causes rat AR protein to fail to interact with mouse proteins or mouse regulatory regions of genes. This becomes an issue particularly in light of the fact that the specification and Applicant's Appeal Brief (page 9, lines 2-4) indicate that the use of the claimed mice is for development of pharmaceuticals. The screening of pharmaceuticals in the claimed mice has no specific and substantial utility because the rat AR has not been disclosed to induce any biological effect in the mice (specification, page 11, lines 19-21). While one may assert that the mice described in the specification may be used to identify compounds that help rat AR interact with a mouse protein or a mouse regulatory region of a gene, the specification does not indicate how compounds identified in this screen has use as a pharmaceutical. That is, neither the specification nor the art provides guidance that inducing a rat protein in a mouse to effect any phenotype has any specific or substantial utility. As such, the claimed mice have no specific and substantial utility.

Applicant indicates that the claimed invention has the credible, specific, and substantial use of studying the tissue selective activity of pharmacological agents by inhibition or activation of androgen receptor that is overexpressed in certain tissues. This is not a study of the properties of the transgenic mouse itself but, rather, a study of

the ability of an agent to inhibit or activate androgen receptor expression in certain tissues. This use is both credible and specific given that, as is well known in the art and stated in the specification, the androgen receptor is a hormone regulated transcription factor that controls the expression of many genetic programs involved in normal physiological processes as well as in pathological conditions such as cancer. In addition, this is a substantial utility in that it is a real world use (i.e., the identification of androgen receptor modulating agents for the treatment of androgen receptor mediated disorders) rather than studying the properties of the claimed transgenic mouse product itself (Appeal Brief, page 9, 2nd parag.). In response, this is not persuasive because as described above, the mice described in the specification have no phenotype and thus, the use of identifying compounds to activate a rat protein to work in a mouse system is not readily apparent.

Thus, the claims remain rejected.

It is noted that the rejection of claims 2, 5, 7, 9, 11, 12, 13 are withdrawn as the art teaches that a transgenic mouse comprising a Pb-mAR transgene construct is a model of human high-grade prostatic intraepithelial neoplasia (see Enablement and 103 rejections below for further discussion).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 18, 19 remain rejected in modified form under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a transgenic mouse comprising in its genome, a transgene construct comprising nucleic acid sequences encoding a reporter protein and mouse androgen receptor (AR) operably linked to a rat probasin promoter, wherein said mouse expresses the transgene construct in the prostate secretory epithelium and wherein mice less than a year old exhibited increases in epithelial proliferation in ventral prostate and dorsolateral prostate and mice older than a year exhibit developed focal areas of intraepithelial neoplasia,

does not reasonably provide enablement for

a transgenic mouse comprising in its genome a transgene construct, wherein said construct comprises nucleic acid sequences encoding a reporter protein and any androgen receptor, other than mouse AR, operably linked to a promoter comprising an androgen response element, other than rat probasin, wherein said androgen receptor and reporter protein is expressed in at least one tissue selected from the group consisting of lung, heart, liver, testis, bone, prostate, and kidney.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has provided a rebuttal in the Appeal Brief, filed March 20, 2007 regarding the rejection of the claims under 112, 1st parag., Enablement. Response to Applicant's rebuttal is provided following the rejection.

As discussed above in the Utility rejection, the specification indicates that the transgenic mice comprising a 2XDR-1 androgen response element are to be used to study the activity of the androgen receptor in different organs of males and females. However, while the specification teaches luciferase expression data (specification, pages 13-14), the specification does not teach that there was any biological effect following expression of the transgene construct in the mice. As such, to use the transgenic mice comprising a 2XDR-1 androgen response element to study the activity of the androgen receptor in different organs of males and females is not readily apparent. Subsequently, to use the mice to study tissue selective activity of pharmacological agents is not readily apparent as the expressed androgen receptor did not appear to have activity in the transgenic mice.

While one may assert that transgenic mice can generally be used to determine what biological responses or phenotype(s) occur following transgene overexpression, the art at the time of filing indicates that an artisan cannot necessarily predict that phenotypes are the result of transgene overexpression. Franz et al., 1997, J. Mol. Med., 75: 115-129 teach that even when an artisan may take into consideration the genetics and regulation of a candidate gene and the tissue/cell type in which the altered expression is carried out in a transgenic animal, an artisan can still run into limitations and difficulties as unexpected results or no effects in the transgenic phenotype occur. Choice of the animal species and unexpected functions of the candidate gene or compensatory alterations of other genes may contribute to these phenomena. In addition to these problems, Franz et al. also indicate that non-specific effects, such as

environment, dietary differences, the genetic background, and positional effects due to the integration of the transgene in overexpression models can modulate the level of gene expression (Franz et al., page 116, 1st col., 3rd parag.). Further, at the time of filing, the art indicates that there are limitations in using transgenic animals as models of disease. Racay, 2002, Bratisl Lek Listy, 103: 121-126, teaches that:

> "mutations of some genes led to phenotype showing severe defects, which did not correspond to any clinically important disorder, indicating either high *in vivo* stability of the gene or the interspecies differences. From the view of human medicine, the differences among the species (it means the differences in genetic background, gene expression, metabolism, and signal transduction) represent the main limitation of the use of genetically modified animals as models of human diseases. Therefore some results acquired by this approach can not be applied in human medicine because of the differences between rodents and human beings (Racay, page 124, under point 5)."

Jakel et al., 2004, Nature Reviews: Genetics, 5: 136-144 provides examples of transgenic mice wherein species-specific differences between the mouse model and human disease are illustrated. In the case of making a rodent model of ALS, Jakel et al. teach that while the human disease is caused by transmission of one mutant copy of the disease, the phenotype in the rodent model is only observed when the mutant human gene is expressed at high copy numbers in the presence of wild-type rodent SOD-1. Jakel et al. teach that the reason for this difference is not clear, but reflects a species-specific attribute that renders rodents less vulnerable to themutant human protein (Jakel et al., page 137, 1st col., 2nd parag.). In the case of making a mouse model of Huntington's disease, Jakel et al. teach that part of the difficulty in making a mouse model likely stems from the species differences of mouse and humans. These species

differences include a rodent's basal ganglia is less vulnerable that its human counterpart, and that basic cellular biology, such as post-translational modification, is different from humans (Jakel et al., page 137, 2nd col., 3rd parag.). Thus, the art at the time of filing clearly establishes the unpredictability of determining the phenotype of transgenic mice even when the activity of the gene has been extensively studied *in vitro*, and further establishes the unpredictability of generating a mouse model for human disease based on the activity of the gene in humans. As these issues apply to the instant invention, while one may assert that a not-yet-discovered phenotype could be exhibited by the transgenic mice comprising a 2XDR-1 androgen response element, the art indicates that an artisan cannot reasonably predict that any phenotype exhibited by the mice necessarily has a relationship with the overexpressed transgene. Rather, to determine whether the relationship between phenotype and transgene is real, an artisan would need to carry out undue experimentation. The experimentation is undue because no guidance is provide in the art or specification that indicates the steps an artisan would need to take to determine whether any phenotype exhibited by a transgenic animal is related to the overexpressed gene.

In a more specific example illustrating that there is unpredictability in arriving at a transgene construct that produces a phenotype associated with a transgene, Stanbrough et al., 2001, PNAS, USA, 98: 10823-10828 teach that young (less than a year old) transgenic mice comprising a transgene construct comprising a nucleic acid sequence encoding mouse androgen receptor (AR) operably linked to a rat probasin promoter exhibit increased levels of epithelial proliferation in the prostate, and mice

older than a year exhibit focal areas of intraepithelial neoplasia strongly resembling human high-grade prostatic intraepithelial neoplasia, a precursor to prostate cancer (PCa) (Stanbrough et al., abstract). In contrast, the specification teaches transgenic mice that comprise a transgene construct (SEQ ID NO. 1), wherein said construct comprises nucleic acid sequences that encode rat AR and luciferase operably linked to a CMV promoter and two DR-1 androgen response elements (2XDR-1) (specification, page 11, lines 9-14; page 15, line 17), and wherein said mice do not develop any abnormality (specification, page 11, lines 19-21). The differences between the mice taught by Stanbrough et al. and that of the specification further illustrate the unpredictability in arriving at transgenic mice that exhibit a phenotype associated with the overexpressed transgene.

In addition to this issue, the specification teaches that the mice described in the specification exhibit no phenotype (specification, page 11, lines 19-21). While the specification indicates that the mice can be used to identify compounds that modulate the AR and be used in pharmaceutical applications, the use of the mice to identify compounds is not readily apparent. While it may be asserted that the claimed mice could be used to screen for drugs that cause a phenotype, it is unclear how identifying a compound that activates or alters rat AR protein such that it effects a biological response in a mouse has an application in other species of animals. The specification and art provide no guidance that whatever biological event that is happening in the transgenic mice comprising rat AR can be readily translated to other biological

situations. As such, the specification provides no guidance for the use of the transgenic mice.

Applicant's arguments filed March 20, 2007 have been fully considered but they are not persuasive.

Applicant indicates that the specification discloses to the skilled worker how to make and use the claimed invention. The arguments detailed in Section A2 of the brief concerning the utility of the claimed invention are relevant to the Enablement rejection (Appeal Brief, page 11, 2nd parag. under point 2). In response, this is not persuasive. As described above in the Utility rejection, the use of the mice described in the specification is not specific and substantial. Again, it is unclear what use the mice described in the specification has when the mice exhibit no phenotype. The specification indicates that the mice can be used to screen for compounds which could then have pharmaceutical applications. However, it is unclear what use the compounds have when there is no disease or disorder to treat in the mice described in the specification. In addition to this issue, while it may be argued that the mice could be used to see what compounds alter rat AR and effect a biological response, neither the art nor the specification provides guidance of similar systems to which the compounds obtained have any application.

As such, the claims remain rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 5, 8, 9, 11, 12, 13 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Stanbrough et al., 2001, PNAS, USA, 98: 10823-10828, in view of Rennie et al., 1993, Mol. Endo., 7: 23-36, and in view of Naylor, 1999, Biochemical Pharmacology, 58: 749-757.

Stanbrough et al. teach a transgenic mouse which comprises a nucleic acid sequence encoding mouse androgen receptor (AR) operably linked to the rat probasin promoter (Pb-mAR). The construct was injected into pronuclei of fertilized mouse eggs (Stanbrough et al., page 10824, 1st col., under "Pb-mAR Transgene Construction"). Stanbrough et al. teach that mice less than a year old exhibited increases in epithelial proliferation in ventral prostate and dorsolateral prostate; mice more than a year old developed focal areas of intraepithelial neoplasia strongly resembling human high-grade prostatic intraepithelial neoplasia, a precursor to prostate cancer (PCa) (Stanbrough et al., abstract).

It is noted that while Stanbrough et al. do not specifically indicate that the claimed mice can be used in a method of screening for modulators of the androgen receptor (e.g. see claim 13), Stanbrough et al. teach that these mice can be used as a model for testing of drugs, diet, or other therapies designed for the prevention of PCa (Stanbrough

et al., page 10827, 2nd col., 4th parag.). It is noted that in the screen for drugs, the screen would encompass a screen for modulators of the androgen receptor.

With regard to the limitation of a promoter comprising an androgen response element, Rennie et al. teach that the probasin promoter, obtained from rat (Rennie et al., page 33, under "Band Shift Assays with the PB Gene"), has 2 androgen response elements (AREs) (Rennie et al., Figures 11 and 12). Note that the rat probasin promoter sequence taught by Rennie, et al., Figure 4, encompasses the promoter used by Stanbrough et al., (-426 to +28 of the probasin promoter) (Stanbrough et al., page 10824, 1st col., under "Pb-mAR Transgene Construction").

While Stanbrough et al. provide this teaching, they do not teach that the transgenic mice or the transgene used in the mice comprise a luciferase reporter gene.

Naylor teaches that reporter gene technology is used to monitor the cellular events associated with gene expression. Naylor teaches that the advantage of using reporter proteins in assays is that they are sensitive, reliable, convenient, and adaptable to large-scale measurements. Naylor teaches that luciferase and green fluorescent protein are popular for non-invasive monitoring of gene expression in living tissues and cells (Naylor, abstract).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made, to include a luciferase reporter gene in the transgene construct taught by Stanbrough et al.

One having ordinary skill in the art would have been motivated to include a luciferase reporter gene in the transgene construct taught by Stanbrough et al. in order

to visualize the cells and tissues that express the transgene construct. Further, motivation is provided by Naylor who teaches that the advantages of using a reporter gene include sensitivity, reliability, convenience and adaptability to large-scale measurements.

There would have been a reasonable expectation of success given the teachings of Stanbrough et al. for teaching transgenic mice comprising in their genome a transgene construct comprising a nucleic acid sequence encoding mouse AR operably linked to a rat probasin promoter, wherein mice less than a year old exhibited increases in epithelial proliferation in ventral prostate and dorsolateral prostate; mice more than a year old developed focal areas of intraepithelial neoplasia strongly resembling human high-grad prostatic intraepithelial neoplasia, a precursor to PCa and wherein Naylor teaches that reporter constructs are used to visualize the tissues and cells that express the transgene construct.

Claims 1, 4, 7, 12 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Stanbrough et al,, 2001, PNAS, USA, 98: 10823-10828, in view of Rennie et al., 1993, Mol. Endo, 7: 23-36, and in view of Naylor, 1999, Biochemical Pharmacology, 58: 749-757 and in view of Webber et al., 1996, The Prostate, 29: 386-394.

As described above, the combined teachings of Stanbrough et al., Rennie et al., and Naylor render the transgenic mouse, cells obtained from the mouse, the transgene construct used to make the mouse, method of making the mouse, and method of using

the mouse to screen for modulators obvious. However, the teachings do not provide guidance for arriving at a prostate cell line obtained from the mouse comprising the Pb-mAR transgene construct.

According to Webber et al., cell lines are useful because cell lines, unlike an in vivo system, provide the opportunity to dissect and separate various actions and interactions and enable the specific actions on the target cell to be pinpointed. Culture models are used for studies on cancer chemoprevention (Webber et al., page 387, 2nd col., 1st parag.). Webber et al. also teach that immortalizing cell lines is an important step carried out on cells as it is difficult to obtain viable samples of human tissue on a routine long-term basis and normal epithelial cells can be maintained as replicative cultures only for a short time before they undergo senesence. Availability of well-characterized, immortalized cell lines provides a uniform, standardized, and reproducible source for study (Webber et al., page 387, 2nd col., 3rd parag.).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made, to make a prostate cell line from the mice comprising the Pb-mAR transgene construct.

One having ordinary skill in the art would have been motivated to make a cell line from the mice comprising the Pb-mAR transgene construct as Webber et al. teach that cell lines are useful in identifying specific actions on a target cell and can be used in studies for cancer chemoprevention.

There would have been a reasonable expectation of success given the teachings of Stanbrough et al. for teaching that the mice comprising the Pb-mAR construct exhibit

focal areas of intraepithelial neoplasia strongly resembling human high-grade prostatic intraepithelial neoplasia, a precursor to prostate cancer (PCa) and for Webber et al. for teaching that cell lines are often obtained to aid an artisan in pinpointing specific actions that occur on a target cell and for studying cancer chemoprevention. With regard to the art teaching the particular embodiments of claim 12, step b, a method of obtaining a cell line from the mouse, wherein the isolated cells are placed under conditions to maintain growth and viability, it is noted that the combined teachings of Stanbrough et al., Rennie et al., Naylor, and Webber et al. meet the limitations of the claim. Webber et al. teach that in order to arrive at a cell line, an artisan would need to immortalize a cell.

Thus, the claims are rejected.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Joanne Hama
Art Unit 1632

PETER PARAS, JR.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600